**The research implementation of the clinical model for evaluating the CYP2C19 allele genotype-guided clopidogrel treatment - Narrative text of presentation**

Konstantine Liluashvili, MD., PhD. Associate Professor, Tbilisi State Medical University, Tbilisi, Georgia.
PI at the Lab Diagnostic Centre of Vistamedi LLC

## Slide #1 (Introductory)

1) I'd like to introduce the evidence from the Research Implementation of the Clinical Model for Evaluating the CYP2C19 allele genotype-guided clopidogrel treatment.
2) I will present outcomes from the clinical study of CYP2C19 genotype-guided clopidogrel treatment in chronic coronary syndrome cases at the post-PCI setting.
3) Key challenges encountered in the Implementation Research, measures to address them and project outcomes will also be presented.

## Slide #2 (Focus)

4) The current evolution of medication therapy has shifted from a 'one-size-fits-all' approach toward a more refined strategy based on personalized risk stratification and treatment.
5) This paradigm has led us toward a more risk-balanced approach to antiplatelet therapy.
6) Modern antiplatelet drugs are essential for the reduction of Major Adverse Cardiovascular Events (so-called MACEs) in the post-PCI setting.
7) Belonging to this class of agents, clopidogrel remains the most commonly prescribed antiplatelet drug despite the newly developed potent platelet inhibitors.
8) In the post-PCI population, dual antiplatelet therapy (so-called DAPT) with the purinergic receptor inhibitor and aspirin remains the standard of care.
9) It ensures optimal medication treatment of chronic coronary syndromes after PCI, de-escalation of antiplatelet treatment, or as a substitute for other agents, including aspirin, in cases of intolerance.
10) So, CYP2C19 genotype-guided medication treatment is actively discussed currently for translating into personalized, risk-balanced antiplatelet therapy, reduction of disease or drug-related adverse clinical events.

## Slide #3 (Practice)

11) According to contemporary guidelines for chronic coronary syndrome management, intensity of platelet inhibition in the post-PCI settings is guided primarily by balancing bleeding risk and subsequently modulated according to ischemic risk.
12) In cases without high ischemic risk features, the default recommendation for six months of dual antiplatelet therapy, typically with Aspirin and Clopidogrel, is provided.
13) In cases of low ischemic risk, shortening of DAPT up to 1–3 months and monotherapy with a platelet inhibitor after abbreviated DAPT.

14) In contrast, in high ischemic and lower bleeding risk, escalation is considered, with prolonged DAPT beyond six months, or monotherapy with a potent platelet inhibitor for long-term secondary prevention, or combined antithrombotic treatment with low-dose a non-vitamin K antagonist oral anticoagulant plus aspirin.
15) For considering antiplatelet responsiveness, genetic testing, particularly CYP2C19 polymorphism analysis, identifies metabolizer status ranging from Ultrarapid to Poor.
16) These insights are especially relevant when considering clopidogrel use, where intermediate or poor metabolizers may require alternative agents such as prasugrel or ticagrelor.
17) Incorporating data on antiplatelet treatment responsiveness ensures that therapy is not only safe but also effective.
18) Despite such considerations, current guidelines do not include direct and strong recommendations for the application of genetic testing for considering drug responsiveness in decision-making.

## Slide #4 (Object)

19) Clopidogrel belongs to a pharmacogenetic actionable drug, mainly through the CYP2C19 gene, which can affect the hepatic metabolism and bioactivation of this pro-drug, leading to lower concentrations of the active metabolite and potential loss of treatment efficacy.
20) The clinical impact of impaired clopidogrel activation spans the spectrum of MACEs presentations, including acute coronary syndromes and PCI, or chronic coronary syndromes, even in the absence of PCI.
21) CYP2C19 genotype-guided medication treatment is actively discussed currently for translating into practice recommendations for emphasizing personalized, risk-balanced antiplatelet therapy.

## Slide #5 (Evidence Base)

22) Recent decades of scientific research have provided valuable evidence supporting CYP2C19 genotype-guided antiplatelet therapy.
23) A systematic review and meta-analysis of 11 randomized controlled and 3 observational studies, with over 20,000 patients, provides robust data on it.
24) The findings demonstrate that tailoring of antiplatelet therapy using CYP2C19 genotyping or platelet function testing yields superior outcomes compared with conventional, unguided clopidogrel treatment, significantly reducing MACEs, Cardiovascular Death, MI, Stent Thrombosis, or Stroke.
25) Meanwhile, CYP2C19 genotype-guided antiplatelet therapy does not increase bleeding risk.
26) Another meta-analysis of seven randomized controlled trials, encompassing nearly 16,000 patients with acute coronary syndromes, provides valuable insights into the comparative effectiveness of clopidogrel versus ticagrelor or prasugrel, stratified by CYP2C19 genotype.

27) Among CYP2C19 loss-of-function allele carriers, ticagrelor or prasugrel significantly reduced ischemic events, while among normal-function allele carriers, clopidogrel demonstrated non-inferiority of outcomes compared with ticagrelor or prasugrel.
28) This evidence suggests that clopidogrel remains an effective therapy in CYP2C19 NFA carriers, avoiding unnecessary exposure to more potent agents associated with bleeding risk.
29) Conversely, in CYP2C19 loss-of-function allele carriers, clopidogrel is inadequate, and prasugrel or ticagrelor should be preferred to reduce ischemic complications.
30) The findings highlight the importance of pharmacogenetics in guiding medication therapy and suggest that personalization can enhance efficacy without compromising safety.
31) This strategy aligns with the broader movement towards precision medicine.

**Slide #6 (CPIC Evidence Base)**

32) Clinical Pharmacogenetics Implementation Consortium guideline updated in 2022 synthesizes high-level evidence from clinical models demonstrating the impact of CYP2C19 genetic variation on clopidogrel pharmacokinetics, pharmacodynamics, and clinical outcomes.
33) CYP2C19 phenotype directly influences clopidogrel metabolism.
34) Intermediate and poor metabolizers consistently demonstrate higher on-treatment platelet reactivity compared with normal or rapid metabolizers, reflecting impaired drug activation.
35) Among intermediate and poor metabolizers, clopidogrel therapy is associated with higher MACEs rates compared with prasugrel or ticagrelor.
36) These alternative agents bypass CYP2C19-dependent activation, providing more consistent platelet inhibition.
37) This evidence strongly supports genotype-guided therapy in clinical practice.
38) A guided antiplatelet strategy declares that prescribing of prasugrel or ticagrelor in intermediate and poor metabolizers, and reserving clopidogrel for normal or rapid metabolizers that reduces the risk of MACEs compared with a conventional clopidogrel strategy.

**Slide #7 (Magnitude)**

39) Despite the compelling evidence and guideline recommendations, real-world prescribing patterns reveal a dominance of clopidogrel.
40) In 2023, clopidogrel accounted for nearly 90% of all P2Y12 inhibitor prescriptions in the United States, while ticagrelor represented just over 10%.
41) Longitudinal data show clopidogrel use has remained stable over the past decade, whereas ticagrelor rose briefly after introduction but has since plateaued.
42) This discrepancy highlights the gap between evidence-based personalization and routine practice, driven by factors such as cost, availability, and clinician familiarity.

**Slide #8 (Purpose)**

43) Despite advances in revascularization and secondary prevention, chronic coronary syndrome clinically manifests multiple risk modifiers and ensures persistence of residual risk, especially in the post-PCI setting.
44) Inter-individual variability in clopidogrel response, largely mediated by CYP2C19 genetic polymorphisms, contributes to differential platelet inhibition and may influence MACE.
45) In the frame of our project, we've planned and conducted a one-year clinical outcomes study comparing CYP2C19 genotype-guided clopidogrel therapy with standard clopidogrel treatment in patients with chronic coronary syndrome following PCI under optimal medication therapy.
46) The central research question asks whether CYP2C19 genotype-guided clopidogrel therapy remains superior to standard clopidogrel treatment when disease-related risk modifiers accelerate disease progression and predispose to MACEs up to one year.

**Slide #9 (Study)**

47) A randomized, parallel-group controlled clinical outcomes study with 12-month follow-up was conducted.
48) Patients were enrolled after elective PCI requiring antiplatelet treatment selection.
49) Chronic coronary syndrome patients with preserved or mildly reduced systolic function intended for clopidogrel-based antiplatelet therapy in the post-PCI setting defined inclusion criteria.
50) Disease/conditions or therapies that limit antiplatelet use or would confound outcome assessment defined exclusion criteria.
51) All participants received guideline-directed optimal medication therapy and structured risk-factor management.
52) From 330 screened patients, 283 were randomized, 200 assigned to CYP2C19 genotype-guided treatment, and 83 assigned to conventional treatment.
53) Of the 200 tested study participants, 157 were identified as normal metabolizers and assigned for CYP2C19 genotype-guided clopidogrel treatment.
54) 43 passive metabolizers were excluded from analysis as they have been intended for antiplatelet treatment with potent platelet inhibitors (ticagrelor or prasugrel) expected to be associated with fewer MACE and frequent bleeding events.
55) All study participants randomised for the genotype-guided or conventional clopidogrel treatment further received DAPT, clopidogrel (or aspirin) plus non-vitamin K antagonist oral anticoagulant, triple antithrombotic therapy, or monotherapy.
56) 15 study participants from genotype-guided treatment and 12 participants from conventional treatment groups did not complete the study follow-up because of participant or physician initiated withdrawal, loss to follow-up, or noncompliance with treatment, and were excluded from the study analysis because of differences in outcomes attributable to antiplatelet treatment non-adherence.

## Slide #10 (Method)

57) We employed RT-PCR-based allelic discrimination assay, so-called TaqMan assay, for genotyping single-nucleotide polymorphisms and used standard procedures for sampling, DNA extraction and genotype differentiation.
58) Using recommended definitions of Clinical Pharmacogenetic Implementation Consortium, clopidogrel metabolizer phenotypes were assigned as normal for normal function allele carriers, and passive metabolizers for loss-of-function allele carriers, including intermediate and poor metabolizers.

## Slide #11 (CYP2C19 Testing)

59) The findings of the study highlighted the clinical utility of CYP2C19 testing.
60) The study results showed that 21.5% of tested participants were identified as carriers of the CYP2C19 LoF alleles.
61) 20.5% were heterozygous carriers of the polymorphic CYP2C19 *2, and only one participant was a homozygous carrier of either the CYP2C19 *2 or CYP2C19 *3 polymorphic allele, underscoring the non-negligible prevalence of impaired metabolizers in the population.
62) The CYP2C19 testing importantly conditioned decision-making on treatment.
63) The genotype-guided approach was applied with dual antiplatelet therapy in 70.5% of cases, and, overall, nearly one-third of cases received combined antithrombotic therapy or monotherapy.
64) In certain applications of treatment options, the frequency of the CYP2C19 gene polymorphism varied from 18.4% to nearly half of the cases carried loss-of-function alleles.
65) The results indicated that the identification of loss-of-function carriers enabled the tailoring of antiplatelet regimens and mitigated the risk of inadequate platelet inhibition.

## Slide #12 (Association Study)

66) Odds ratio analysis of the CYP2C19 genotype-guided treatment to 12-month clinical outcome showed significant positive effects on certain clinical outcomes.
67) Odds ratios below 0.5 were significant for recurrent angina, repeated revascularization, all-cause hospitalization, and composites of net adverse clinical events or major adverse cardiovascular or cerebrovascular events.
68) Odds ratios below 1 were found for all-cause or CVD death, nonfatal MI, HF event or Stroke/TIA, but without significant associations.
69) These data support integrating genotype information into personalized antiplatelet strategies for patients undergoing PCI.

## Slide #13 (Risk modifiers exposure)

70) Aside from differently approached clopidogrel-based treatment, genotype-guided versus conventional, all participants received equally optimal medication treatment.

71) The significantly higher rates of certain clinical outcomes were observed in ‘unspecified’ metabolizers than in ‘normal’ metabolizers.
72) The study results showed the almost uniform patterns of adverse clinical outcomes in both groups.
73) The emerged disease-related risk modifiers showed strong and significant associations (adjusted OR > 2 and $p < 0.05$) to key clinical endpoints.
74) We considered that the possible exposure of multiple clinical modifiers of risk may interfere with outcomes in both groups.
75) These study results require a deeper analysis to explain them in further research.

**Slide #14 (Findings)**

76) So, if summarize, the study revealed useful findings.
77) A high frequency of the CYP2C19 LoF *2, affecting approximately one-fifth of the tested population and reflecting optimal medication treatment schemes;
78) The efficiency of CYP2C19 genotype-guided antiplatelet therapy exceeds that of standard clopidogrel-based treatment for preventing early hospitalization, NACE, MACCE, recurrent angina, repeated revascularization.
79) The significant practical value of CYP2C19 genotyping for the precision of antiplatelet therapy positions it into routine laboratory diagnostic workflows.
80) Clinical outcomes might be exposed to disease-related risk modifiers that appear due to dysmetabolism, comorbidities, structural and functional myocardial dysfunction, or coronary lesion anatomy.

**Slide #15 (Challenges)**

81) When we planned the study and started the project implementation, we identified the main challenge and found it too complex.
82) It can be explained with:
83) Unawareness of gene-to-drug interactions, driven by insufficient understanding of pharmacogenetics and the benefits of genotype-guided treatments among health professionals and patients;
84) Lack of strong guideline recommendations for routine clinical practice provides significant doubt regarding the implementation of personalized, genotype-guided medication treatments.
85) Furthermore, misunderstandings about the role of laboratory diagnostic practices in personalized medicine and clinical decision-making, a lack of effective bridging between medical and laboratory practices, as well as concerns about the additional costs and reimbursement pathways, contribute to a lack of willingness to adopt a genotype-guided treatment approach in real-world clinical settings.

**Slide #16 (Project)**

86) Through such discussions, we aimed to develop an implementation research project for evaluating CYP2C19 genotype-guided antiplatelet treatment outcomes in real-world clinical practice.

87) Implementation-specific objectives included:
88) Integrating existing evidence base;
89) Developing a study protocol for CYP2C19 genotype-guided, antiplatelet therapy in chronic coronary syndrome following PCI;
90) Implementing procedures for real-world practice outlined in the study protocol;
91) Evaluating outcomes of genotype-guided versus standard antiplatelet treatment;
92) Improving awareness and understanding of gene-drug interactions, genotype-guided treatment, and the vital role of laboratory services in achieving better outcomes through the dissemination of the study findings to inform professional societies and stakeholders.

**Slide #17 (Project Initiation)**

93) For the project initiation, we provided the methodological and procedural applications of CYP2C19 *2, *3 genotyping in the existing laboratory practice, which further served as the central laboratory for the clinical study.
94) We set up measurements, probed the tests in healthy and CVD patient volunteers, and defined Quality and Safety Procedures.
95) To ensure the scientific rigor of expected study results, we developed the study protocol to fit existing clinical procedures and regulatory issues of real-world practice and adjust pre-analytical procedures and post-analytical CYP2C19 genotyping results' delivery.
96) We obtained ethical approval from the national level IRB and completed prospective registration of the study protocol at NIH NLM ClinicalTrial.gov.

**Slide #18 (Involvement)**

97) Along with the Central laboratory diagnostic, four specialized clinical centers providing ambulatory and hospital health care services at the post-PCI setting were involved in the study implementation.
98) We established a study data management team and a scientific advisory group for the clinical study.
99) The medical team of each center was trained on issues presented in the study protocol through delivering bites of evidence from recently published impactful clinical studies and informing them on CYP2C19 genotyping procedures.

**Slide #19 (Publications)**

100) After completing the active study component of the project, we updated the results on the NIH NLM ClinicalTrials.gov PRS system.
101) We submitted abstracts highlighting the project and its findings to impactful global scientific conferences.
102) One was presented as a poster and published in the conference supplements.
103) Another will be presented at the poster session in the near future.
104) Currently, a manuscript for the scientific publication displaying 'CYP2C19 Genotype-Guided Antiplatelet Clopidogrel Treatment of Chronic Coronary

Syndromes after Elective Percutaneous Coronary Intervention' and presenting the key study results, is being prepared.

105) Additionally, we are preparing another manuscript that will analyze the cost-benefits of CYP2C19 genotype-guided antiplatelet clopidogrel treatment.

## Slide #20 (Presentations)

106) Throughout the project implementation, in close collaboration with academic institutions, we delivered a series of oral presentations and lectures to highlight key themes, including the clinical application of pharmacogenomics, CYP2C19 genotype-guided clopidogrel treatment, and outlines of antiplatelet treatment at conferences of authoritative national professional societies, academia and other stakeholders.

## Slide #21 (Project Outcomes)

107) If summarize project outcomes:
108) We've piloted clinical and lab diagnostic procedures for genotype-guided treatment in real-world clinical practice;
109) We've achieved a more expanded understanding of the pharmacogenetic approach to efficiency and safety of drug treatment, and CYP2C19 genotype-guided clopidogrel therapy;
110) We've improved awareness of the professional community regarding the critical role of laboratory medicine in healthcare outcomes;
111) We've promoted a pharmacogenetic approach to medication treatment, precision medicine and personalized, patient-centred healthcare in the larger context.

## Slide #22 (Further research)

112) As we look ahead, several critical research directions emerge for advancing pharmacogenetics in clinical practice.
113) First, we must strengthen genotyping strategies through the application of comprehensive panels, e.g. a cardiac pharmacogenetic panel tests, which can further enhance both efficiency and safety of drug treatment.
114) Beyond individual genes, the integration of drug–drug interaction data will be essential for truly informed prescribing decisions.
115) Second, we need to identify molecular markers within key signaling systems that act as modifiers of cardiovascular risks.
116) Using of these markers will improve our ability to predict major adverse events and refine patient stratification.
117) Third, harmonizing and standardizing pharmacogenetic testing systems is vital.
118) This includes laboratory methods, quality assurance, and analytics.
119) Without consistency, results cannot be reliably translated into clinical practice.

120) And Finally, we must invest in knowledge infrastructure that means building a robust evidence base collection, developing continuing professional development programs, and establishing comprehensive data registries.
121) Together, these elements will ensure that pharmacogenetics is not just a research tool, but a cornerstone of everyday clinical decision-making.